Remarks

The present response is submitted in reply to the Office action issued on June 13, 2006. Claims 1-65 are pending in this application. Claims 1-24, 43, 44, 46, 47 and 63-65 are withdrawn from consideration. Claim 45 is canceled. Claims 66 and 67 are newly added herewith. Support for new claims 66 and 67 may be found throughout the specification, such as at paragraph ([000068]). No new matter has been added.

The Applicant wishes to thank the Examining Attorney for entering the previously filed amendments to the specification and claims. The Applicant also wishes to thank the Examining Attorney for the withdrawal of the objection to the declaration/oath, the objection to the specification and the various objections and rejections to the claims which had been set forth in the previous Office action. However, reconsideration of the new grounds of rejections is respectfully requested in light of the following remarks.

Rejection of Claims 25-33, 38, 49-54 and 58 under 35 U.S.C. 102(b)

Claims 25-33, 38, 49-54 and 58 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,204,033 (Müller-Schulte), in view of Kondo, et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp. 337-341). Although the rejection is set forth under Section 102(b), it is believed the rejection should in fact have been set forth under Section 103(a). Therefore, the Applicant respectfully responds to the present rejection as if it were made under Section 103(a).

The Examiner argues that Müller-Schulte teaches a process for a production of polymers containing at least one of magnetic or metallic colloids, the process comprising the steps of dispersing at least one of encapsulated magnetic or metallic colloids in an

aqueous monomer solution, suspending the aqueous monomer solution in an organic phase that is not miscible with water after addition of a radical initiator and radically polymerizing the organic phase to nano- or micro- particles (Abstract and col. 7, lines 19-55). However, the Examiner notes that Müller-Schulte fails to teach a process wherein the monomer solution contains a thermosensitive monomer suspended through mechanical communition and further adding a cross-linking agent to form thermosensitive polymers having a physical structure changeable by magnetic induction.

The Examiner relies on Kondo, et al. for the teaching of a method of polymerizing magnetic particles by co-polymerizing N-isopropylacrylamide (NIPAM), methacrylic acid (MAA) and N,N'-methylene-bis-acrylamide (MBA, Abstract). The Examiner states that crosslinking agent MBA is used to increase the mechanical strength of the microspheres and that the polymerization process involves stirring (i.e., mechanical communition) of a suspension of monomers, crosslinking reagent and a radical initiator, such as potassium persulfate.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of invention to include the method of polymerizing encapsulated magnetic particles of Müller-Schulte by suspension of NIPAM, MAA and MBA through mechanical communition after adding a crosslinking reagent and a radical initiator as taught by Kondo, et al. in order to generate thermosensitive polymeric particles having a physical structure changeable by magnetic induction. The Examiner further concludes that there would have been a reasonable expectation of success since Müller-Schulte

demonstrates that the encapsulated microparticles can be further polymerized.

The applicant respectfully submits that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all of the claim limitation. Applicant respectfully submits that one skilled in the art would have no suggestion or motivation to combine the aforementioned references in order to arrive at the present invention. Additionally, even if one skilled in the art were to consider Müller-Schulte alone, or in combination with any of the other prior art references, et al., each and every limitation of the present invention would not be disclosed, nor would there be a reasonable expectation of success if the aforementioned references were to be considered. Still further, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention (M.P.E.P. 2141.02 VI; *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)).

The Applicant respectfully submits that the present invention is patentably distinct from the aforementioned combination of teachings. Moreover, the Applicant submits that there would have been no motivation for one skilled in the art to have referred to Müller-Schulte alone or in combination with any other prior art, in order to have arrived at the present invention. Still further, each and every feature of the present invention as recited in the present claims are not taught or disclosed in Müller-Schulte in combination with

Kondo, et al.

The Applicant respectfully submits that, as noted in the previous Office action response, the Müller-Schulte reference relates to a process for producing polyvinyl alcohol (PVAL) particles containing a magnetic colloid encapsulated inside. The reference does not teach or disclose that these polyvinyl alcohol particles are thermosensitive or whether they have a physical structure changeable by magnetic induction, as required by instant claims 25 and 26. Furthermore, Müller-Schulte fails to teach or disclose "thermosensitive polymers." Müller-Schulte basically discloses polyvinylalcohol-carriers which are neither thermosensitive, nor carriers for active compounds. Müller-Schulte teaches an oil-suspension process which one skilled in the art would clearly recognize could not be transferred to N-isopropylacrylamide-based products or to a process for the formation of such products.

Müller-Schulte teaches that the alcohol particles are prepared by dispersing a magnetic colloid in an aqueous polymer (PVAL) solution and adding this mixture to an organic phase (such as an oil phase). While the mixture is stirred to suspend the aqueous polymer solution in the oil phase, a bi-functional cross-linking agent is added to cross-link the polymer chains of the PVAL. This results in PVAL particles having a magnetic colloid encapsulated inside (Abstract; claim 1; col. 5, line 58 – col. 6, line 49; Example 1). The particles disclosed in Müller-Schulte are essentially obtained by the cross-linking of a pre-existing polymer, namely, polyvinyl alcohol.

The Examiner also states in section 16 of the Office action that Müller-Schulte

discloses suspending the aqueous monomer solution in an organic phase that is not miscible with water after addition of a radical initiator and radically polymerizing the organic phase to nano- or micro-particles. However, this description of Müller-Schulte relates to the optional grafting process which may be performed after having prepared PVAL particles, as described above. This grafting process is described in Müller-Schulte at col. 7, lines 19-55, in claim 14 and in Example 24.

The Applicant further submits that according to the process steps defined in present claims 25 and 26, the cross-linking agent and the radical initiator are present simultaneously within the polymerization reaction mixture. To the contrary, when performing the graft polymerization step recited at the end of the Abstract of Müller-Schulte, the cross-linking agent that was initially used for cross-linking the PVAL is no longer present, and no additional cross-linking agents are added. In the radical polymerization reaction (also referred to as "grafting" in Müller-Schulte), the reaction mixture contains only PVAL particles (acting as the grafting substrate), vinyl monomers and cerium salt as a polymerization initiator (see Example 24, and col. 7, lines 19-35 of Müller-Schulte). No cross-linking agent is added to this reaction mixture. Although a cross-linking agent is initially used for cross-linking the polyvinyl alcohol chains to generate the polymer particles (Example 1; glutaraldehyde as a cross-linker), this cross-linker is no longer present at the time when the grafting reaction is performed. The remaining free cross-linker molecules that were not incorporated into the cross-linked PVAL polymer particles are removed during the washing steps performed prior to the grafting reaction (see Example 24 of Müller-Schulte). Moreover, for the purpose of the

grafting reaction, the presence of cross-linking agents would not even make any sense and would even be detrimental to the reaction. In summary, as noted by the Examiner, Müller-Schulte fails to teach the presence of a multifunctional cross-linking agent during the radical polymerization.

In other words, the technology for manufacturing PVAL according to Müller-Schulte is principally different from the technology of the present invention. In particular, as noted above, the subject of Müller-Schulte are graft polymers for modifying the surface of PVAL beads by using CER-salts as catalysts. On the other hand, the polymerisation according to the presently claimed invention is initiated by a N,N,N',N'-tetramethyl-ethylendiamin / peroxide system to produce the presently claimed beads, as set forth in the present specification (paragraph [000068]); claims 25, 26, 66 and 67). It is respectfully submitted that it would be clear to one skilled in the art that the reaction using CER-salts of Müller-Schulte would not be applicable to the process for producing the presently claimed invention.

Kondo, et al. fail to make up for the aforementioned deficiencies of Müller-Schulte. In particular, Kondo, et al. describe a coprecipitation process. According to the presently claimed invention, the active compounds are encapsulated by an inverse suspension technique. In contrast thereto, Kondo, et al. teach the active compounds are only accumulated rather than encapsulated. Moreover, it would be clear to one skilled in the art that the process of Kondo, et al. would not be applicable as a carrier for active compounds since the active compounds in the secondary reference are not encapsulated.

In light of the aforementioned deficiencies of the combination of teachings of Müller-Schulte and Kondo, et al., the Applicant respectfully submits that the combination of references fails to teach every limitation set forth in the presently rejected claims and that due to these deficiencies, one skilled in the art would not have been motivated to combine these references to arrive at the present invention. Withdrawal of this rejection is strongly requested.

Rejection of Claims 34 and 55 under 35 U.S.C. 102(b)

Claims 34 and 35 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,204,033 (Müller-Schulte), in view of Kondo, et al., as applied to claim 25 above, and further in view of U.S. Patent No. 5,990,262 (Shishikura, et al.). Although the rejection is set forth under Section 102(b), it is believed the rejection should also in fact have been set forth under Section 103(a). Therefore, the Applicant respectfully responds to the present rejection as if it were made under Section 103(a).

The Examiner argues that Müller-Schulte in view of Kondo, et al. teaches a process for a production of thermosensitive polymers, as discussed above and that Müller-Schulte further teaches that organic solvents such as hexane, heptane, cyclohexane or petroleum ether are used in the process for the production of thermosensitive polymers. However, the Examiner notes that Müller-Schulte fails to specifically disclose that these organic phase solvents have a polar solubility parameter of 5-10 $(cal/cm^3)^{1\,2}$.

The Examiner refers to Shishikura, et al. for the teaching that heptane has a solubility parameter of 7.4 $(cal/cm^3)^{1\,2}$. Therefore, the Examiner concludes that one of

ordinary skill in the art would recognize that the organic solvent of Müller-Schulte would inherently have solubility parameter of 7.4 $(cal/cm^3)^{1\,2}$.

The Applicant respectfully disagrees with this rejection for at least the above-discussed deficiencies of Müller-Schulte in view of Kondo, et al. Moreover, Shishikura, et al. clearly fail to make up for any of said deficiencies of Müller-Schulte in view of Kondo, et al. As noted above, Müller-Schulte relates to a grafting process using pre-existing polymer particles as a substrate (col. 7, lines 19-51). This process is performed in the presence of cerium salts and in the absence of cross-linking agents. The solvents set forth in column 7 of Müller-Schulte are used for a different purpose than in the present invention.

In addition, Shishikura, et al. discloses polymers which are polycarbonate-based. One skilled in the art would readily recognize that polycarbonates are neither soluble in water nor include comparable properties to either N-isopropylacrylamides or N-substituted acrylamides, in accordance with the presently claimed invention (see for example, paragraph [000046] of the present specification). In contrast to the polycarbonates, the thermosensitive polymers of the invention are forming gels with a water content of greater than 80%. It is respectfully submitted that one skilled in the art would therefore recognize that polycarbonates as discussed in Shishikura, et al. would not be suitable for forming the thermosensitive polymer beads according to the present invention.

Therefore, because each and every feature of the present invention as recited in

claims 34 and 55 are not taught or disclosed in Müller-Schulte in view of Kondo, et al., even when taken in consideration of Shishikura, et al., each and every limitation of the present invention is not taught or disclosed and so the reference (or combination of references) does not render the present invention obvious. It is respectfully requested that this rejection be withdrawn.

Rejection of claims 35, 36, 56 and 57 under 35 U.S.C. 103(a)

Claims 35, 36, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo, et al. as applied to claims 25 and 26 above, and further in view of U.S. Patent No. 4,647,536 (Klaveness, et al.). According to the Examiner, Müller-Schulte in view of Kondo, et al. teaches a process for a production of thermosensitive polymers as discussed above, but fails to teach a process further comprising the step of adding at least one surfactive substances to the organic phase at 0.05 to 0.15% by weight, wherein the surfactive substance is polyoxyethylenes.

The Examiner relies on Klaveness, et al. for the teaching of using surfactants such as polyoxyethylenes typically in amounts of 1-10% w/v to stabilize the resulting oil in water emulsion during emulsification process for making polymeric particles (col. 11, lines 21-56).

The Examiner thus concludes that it would have been obvious to one of ordinary skill in the art to include polyoxyethylenes as a surfactant in 1-10% w/v in the suspension of magnetic colloids and monomers of Müller-Schulte in view of Kondo, et al. with those as taught by Klaveness, et al. in order to stabilize the suspension of aqueous monomer solution in non-miscible organic phase during emulsification process. The Examiner

further concludes there would have been a reasonable expectation of success since an addition of a surfactant such as polyoxyethylenes would stabilize the suspension of aqueous monomer solution in non-miscible organic phase in a method for forming polymeric particles.

The Applicant again disagrees with the Examiner's rejection for at least the numerous deficiencies of Müller-Schulte in view of Kondo, et al. which have been discussed above. The teachings of Klaveness, et al. fail to make up for any of the many deficiencies of Müller-Schulte in view of Kondo, et al. In particular, Klaveness, et al. teach polymer carriers which can be used as contrast agents. The Applicant respectfully submits that one skilled in the art would recognize that such compounds are different from the thermosensitive polymers of the present invention and that, in turn, the polymer carrier cannot be used for encapsulation of magnetic compounds or active compounds of the invention. In addition, inductive warming for the release of the compounds would not be possible.

In light of the aforementioned deficiencies of the combination of teachings of Müller-Schulte, Kondo, et al. and Klaveness, et al., the Applicant respectfully submits that the combination of references fails to teach every limitation set forth in the presently rejected claims and that due to these deficiencies, one skilled in the art would not have been motivated to combine these references to arrive at the present invention. Withdrawal of this rejection is strongly requested.

Rejection of claim 37 under 35 U.S.C. 103(a)

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-

Schulte in view of Kondo, et al., as applied to claim 25 above, and further in view of U.S. Patent No. 5,415,931 (Minghetti, et al.). The Examiner argues that Müller-Schulte in view of Kondo, et al. teaches a process for a production of thermosensitive polymers as discussed above, but fails to teach a production of thermosensitive polymers further comprising a step of pre-polymerizing the monomer solution for 5-120 second before dispersion in the organic phase.

The Examiner refers to Minghetti, et al. for the teaching of pre-polymerizing a portion of monomers before final polymerization process in order to more readily control the polymerization process and the size and shape of the polymer (col. 1, lines 27-33).

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to include in the method of Müller-Schulte in view of Kondo, et al. an additional step as taught by Minghetti, et al. in order to arrive at the present invention as claimed in claim 37.

The Applicant disagrees with the Examiner's rejection for at least the numerous deficiencies of Müller-Schulte in view of Kondo, et al., which have been discussed at length above. Moreover, Minghetti, et al. fail to make up for the deficiencies of Müller-Schulte in view of Kondo, et al. As noted above, Müller-Schulte fails to teach a process by which thermosensitive polymers can be obtained by suspending an aqueous monomer solution, which also contains magnetic or metallic colloids, in an organic phase that is not miscible with water, after adding a multifunctional cross-linking agent and a radical initiator, and by polymerizing this reaction mixture.

Minghetti, et al., on the other hand, teach acrylsheets which can be made of an

acrylester. It would be apparent to one skilled in the art that the process for making such products would not be applicable to the process for preparing spherical particles and for encapsulating active compounds of other fluids, in accordance with the presently claimed invention.

In light of the aforementioned deficiencies of the combination of teachings of Müller-Schulte, Kondo, et al. and Minghetti, et al., the applicant respectfully submits that the combination of references fails to teach every limitation set forth in the presently rejected claims and that due to these deficiencies, one skilled in the art would not have been motivated to combine these references to arrive at the present invention. Withdrawal of this rejection is strongly requested.

Rejection of claims 39, 40, 59 and 60 under 35 U.S.C. 103(a)

Claims 39, 40, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo, et al. as applied to claims 25 and 26 above, and further in view of U.S. Patent No. 6,204,033 (Mosbach, et al.).

According to the Examiner, Müller-Schulte in view of Kondo, et al. fails to teach a process for a production of thermosensitive polymers, further comprising a step of encapsulating active agents in the polymers by adding the active agents to a monomer solution containing at least one of magnetic or metallic colloids.

The Examiner refers to Mosbach, et al. for the teaching of a method of encapsulating enzymes by bead polymerization process, where the monomer solution together with enzyme is dispersed in hydrophobic phase (col. 1, lines 31-34).

The Examiner thus concludes that it would have been obvious to arrive at the

presently claimed invention by including a step of adding encapsulating active agents (enzymes) in the polymers by adding the active agents to a monomer solution containing at least one of magnetic or metallic colloids of Müller-Schulte in view of Kondo, et al. as taught by Mosbach, et al. The Examiner also concludes that there would have been a reasonable expectation of success since Mosbach, et al. demonstrated that encapsulating active agents such as enzymes (proteins) can be performed during the polymerization step.

The Applicant again respectfully disagrees with the Examiner's rejection for at least the numerous deficiencies of Müller-Schulte in view of Kondo, et al., which have been discussed above. Moreover, Mosbach, et al. fail to make up for the aforementioned deficiencies of Müller-Schulte in view of Kondo, et al.

Mosbach, et al. teach carriers which are agarose-based for encapsulation. In contrast to the polymers of the present invention, the polymers cited in Mosbach, et al. are not applicable since they are not thermosensitive polymers in accordance with the presently claimed invention. Moreover, Mosbach, et al. fail to teach magnetic compounds which are encapsulated which can be heated by induction for releasing active compounds. According to the process for preparing the beads of Mosbach, et al. by gelation, only beads which are 0.1 – 1.0 mm are obtainable, in contrast to the present invention.

In light of the aforementioned deficiencies of the combination of teachings of Müller-Schulte, Kondo, et al. and Mosbach, et al., the applicant respectfully submits that the combination of references fails to teach every limitation set forth in the presently rejected claims and that due to these deficiencies, one skilled in the art would not have been motivated to combine these references to arrive at the present invention. Withdrawal

of this rejection is strongly requested.

Rejection of Claims 41, 42, 61 and 62 under 35 U.S.C. 103(a)

Claims 41, 42, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo, et al. and of Mosbach, et al. as applied to claims 40 and 60 above, and further in view of U.S. Patent No. 4,413,797 (Khan, et al.).

According to the Examiner, Müller-Schulte in view of Kondo, et al. fails to teach a process for a production of thermosensitive polymers, further comprising a step of adding a compound selected from the group consisting of polyvalent alcohols, polyvinyl alcohols, gelatins and carbohydrates which are added to the active agents in an amount of 0.1 to 2.0% by weight, wherein the polyvalent alcohols or carbohydrates are selected from the group consisting of inosite, mannite, sorbite, aldonite, erythrite, sucrose, glycerine, xylite, fructose, glucose, galactose and maltose.

The Examiner refers to Kahn, et al. for the teaching of adding a stabilizer to an active agent (ACTH) (col. 7, lines 26-37) and concludes that it would have been obvious to arrive at the presently claimed invention by adding the stabilizer as taught by Khan, et al.

The Applicant respectfully disagrees with the Examiner's rejection for at least the numerous deficiencies of Müller-Schulte in view of Kondo, et al. and Mosbach, et al., which have been discussed above. Moreover, Kahn, et al. also fail to make up for the aforementioned deficiencies of Müller-Schulte in view of Kondo, et al. and Mosbach, et al.

Kahn, et al. teach polymer microbeads for the release of ACTH. The carrier is

produced by polyactid which can be prepared by "spray drying." The Applicant respectfully submits that it would be clear to one skilled in the art that it is not possible to prepare the magnetic compounds of the present invention by a process of "spray drying" as described in Kahn, et al. In particular, the carrier described in Kahn, et al. can not be heated by magnetic induction. This process of Kahn, et al. is completely different from the process of the present invention and one skilled in the art would not have referred to said process for overcoming the deficiencies of Müller-Schulte in view of Kondo, et al. and Mosbach, et al.

In light of the aforementioned deficiencies of the combination of teachings of Müller-Schulte, Kondo, et al., Mosbach, et al. and Kahn, et al., the applicant respectfully submits that the combination of references fails to teach every limitation set forth in the presently rejected claims and that due to these deficiencies, one skilled in the art would not have been motivated to combine these references to arrive at the present invention. Withdrawal of this rejection is strongly requested.

Double Patenting

The Examiner has set forth numerous double-patenting rejections. In summary, the Examiner has (1) rejected claims 25-33, 38, 49-54 and 58 as being unpatentable on the ground of nonstatutory obviousness-type double patenting over claims 1-9 and 14 of Müller-Schulte in view of Kondo, et al.; (2) rejected claims 34 and 55 over claims 1-9 and 14 of Müller-Schulte in view of Kondo, et al., as applied to claim 25 above, and further in view of Shishikura, et al.; (3) rejected claims 35, 36, 56 and 57 over claims 1-9 and 14 of Müller-Schulte in view of Kondo, et al., as applied to claims 25 and 26 above, and further

in view of Klaveness, et al.; (4) rejected claim 37 over claims 1-9 and 14 of Müller-Schulte in view of Kondo, et al., as applied to claim 25 above, and further in view of Minghetti, et al.; (5) rejected claims 39, 40, 59 and 60 over claims 1-9 and 14 of Müller-Schulte in view of Kondo, et al., as applied to claims 25 and 26 above, and further in view of Mosbach, et al.; and (6) rejected claims 41, 42, 61 and 62 over claims 1-9 and 14 of Müller-Schulte in view of Kondo, et al. and Mosbach, et al., as applied to claims 40 and 60 above, and further in view of Khan, et al.

The merits set forth by the Examiner for combining each of the respective groups of prior art references have been discussed above in relation to the numerous obviousness rejections. The Examiner essentially argues that although the conflicting claims are not identical, they are not patentably distinct from each other.

The Applicant disagrees with the Examiner's double patenting rejections for at least the numerous deficiencies of Müller-Schulte, which have been discussed above. To reiterate, Müller-Schulte does not teach a process for producing thermosensitive polymers, and the process of Müller-Schulte does not comprise dispersing magnetic or metallic colloids in an aqueous monomer solution. Moreover, the particles of Müller-Schulte are not generated by radical polymerization of monomers, but rather by cross-linking of PVAL polymers.

Clearly, the process of Müller-Schulte is fundamentally different from that of the presently claimed invention, and therefore the Applicant submits that the claims of Müller-Schulte cannot be interpreted as encompassing the claims of the present application. The claims of Müller-Schulte do not pertain to a process for producing thermosensitive

polymers by radical polymerization of monomers.

Müller-Schulte discloses polyvinylalcohol-carriers which are neither thermosensitive nor carriers for active compounds and teaches an oil-suspension process which cannot be transferred to a process for producing N-isopropylacrylamide-based products. Therefore, the Applicant strongly requests that the double-patenting rejection be withdrawn.

Conclusion

In light of the foregoing claims and arguments, it is believed that the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

Date: October 5, 2006

By: _____
D. Peter Hochberg
Reg. No. 24,603

D. Peter Hochberg Co., L.P.A.
1940 E. 6th St. – 6th Floor
Cleveland, OH 44114
(216) 771-3800
DPH/SM